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Subacute sclerosing panencephalitis

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Introduction

Subacute sclerosing panencephalitis (SSPE) is a rare disease which predominantly affects children of school age. The clinical features include an insidious afebrile onset with behavioural disturbance and progressive dementia sometimes associated with epilepsy. Later akinetic mutism and myoclonic jerks with pyramidal and extrapyramidal signs appear. Finally there is progressive decortication leading to death within months or at most 2 years. Spontaneous recovery though very rare has been reported (Pearce & Barwick, 1964; Cobb & Morgan-Hughes, 1968; Resnick, Engel & Sever, 1968). There is a paretic colloidal gold curve in the cerebrospinal fluid (CSF) but the cell count and protein are usually within normal limits. The electroencephalogram records taken early in the illness may not show periodic complexes but these typically occur later. The interval between the bilateral high amplitude slow wave complexes diminishes as the disease progresses. The record may be more abnormal on one side than the other with some clinical and radiological features suggesting a space-occupying lesion. Finally the clinical diagnosis may be confirmed by taking a brain biopsy during life.

The aetiology of SSPE has remained obscure until recently and a conference was held in 1967 to review the evidence for a viral aetiology of the disease (Sever & Zeman, 1968). We may now consider the contributions of light and electron microscopy, virology and immunology towards the elucidation of of the aetiology of this disease.

Microscopy

The viral aetiology of SSPE was suggested by the finding of Cowdry type A nuclear inclusions in brain cells (Dawson, 1933). Many early investigators assumed that the Cowdry type A inclusions indicated infection with herpes simplex virus but it is now known that the measles–distemper–rinderpest groups of viruses form similar inclusions in the nucleus and cytoplasmic inclusions in addition.

Three boys aged 12 years, 15 years and 17 years were investigated by Connolly *et al.* (1967). They had had childhood measles at the ages of 8 months, 3 years and 4 years respectively which meant that there was a latent period of 11–13 years between their childhood measles and the onset of SSPE. Death occurred in the three boys after illnesses lasting 17 months, 6 months and 3 months respectively. The boys had no history of measles in the months before the onset of their terminal illness and none had any contact with each other. They had not received either killed or live attenuated measles vaccines.

The histology of the brains of the three patients showed eosinophilic nuclear and cytoplasmic inclusions in neurones and glial cells, and Cowdry type A inclusions were present. The methyl green–pyronin stain showed that the inclusions contained ribonucleic acid (RNA) which was consistent with an RNA virus such as measles being present. Deoxyribonucleic acid (DNA) could not be found in the inclusions by the Feulgen reaction, which excluded herpes simplex or varicella-zoster viruses being present since they contain DNA (Connolly *et al.*, 1968).

Further support for the viral aetiology of SSPE came from electron microscopic studies of the brain by Bouteille *et al.* (1965) who found intranuclear tubular filaments which resembled those seen in the dog kidney cells infected with measles virus (Tawara, 1965). These observations have been confirmed by many others (Herndon & Rubinstein, 1968) but it should be pointed out that it is impossible to identify a particular virus such as measles on electron microscopy alone since its structure resembles that of other viruses of the paramyxovirus group such as distemper, rinderpest, mumps, parainfluenza types 1, 2, 3, 4, Newcastle disease virus and the bovine and simian paramyxoviruses.

Virology

The first definite evidence linking measles virus with SSPE came from the observations of Connolly *et al.* (1967) who found measles antigen in the brains of the three patients described above and measles antibody in their sera and CSF. In the cerebral cortex of the three patients both nuclear and cytoplasmic measles specific staining was found in neurones and glial cells by the direct immunofluorescence test. Oval or round fluorescent masses surrounded by a ring of fluorescent granules similar to type A inclusions were common and binucleate fluorescing cells which were probably astrocytes were also seen. There was no staining of the brains with conjugated antidistemper serum (Connolly, 1968; Freeman *et al.*, 1967).

Many attempts have been made to isolate virus from the brain in this disease but without success until recently. There is one report of transmission of encephalitis from brain biopsy material to cynomolgous monkeys (Perier *et al.*, 1968) but Connolly *et al.* (1967) were unable to isolate virus from the brains of the three SSPE patients in rhesus monkeys, mice and cell cultures.

Intracerebral inoculation of ferrets with brain suspensions from three children with SSPE produced a subacute encephalitis in 5 months and passage of infected ferret brain reproduced the disease in 3 months, but evidence of measles virus infection could not be found (Katz *et al.*, 1968). Later Katz *et al.* (1970) inoculated ferrets with SSPE brain cell cultures which produced encephalitis in only 2 weeks and was associated with evidence of measles virus infection. Koprowski, Barbanti-Brodano & Katz (1970) reported finding Papova-like particles (tumour viruses) in the cytoplasm of cultured human brain cells from SSPE in addition to paramyxovirus (measles) nucleocapsids but it is not yet known whether the tumour virus particles were unobtrusive symbionts present in the brain tissue or if they are capable of causing disease with or without the help of measles virus.

Baublis & Payne (1968) described the occurrence of measles antigen and syncytia formation in SSPE brain cell cultures and the production of syncytia in several kinds of cultured cells when exposed to these brain cells, while Horta-Barbosa *et al.* (1969) isolated measles virus from SSPE brain by cocultivation of cultures of brain biopsy fibroblasts with HeLa cells. A later report by Horta-Barbosa *et al.* (1971) showed that suppressed measles virus infection in SSPE is not restricted to the brain alone. Measles virus was isolated by cocultivation of cultures of lymph node biopsies with HeLa cells from two patients in the early stages of SSPE. Measles virus was not isolated by these techniques from three patients in the late stages of SSPE or from five control patients. It is of interest that Dayan & Stokes (1971) found measles virus antigen by immunofluorescence in cells from CSF in four patients with SSPE which suggests that cells of the lymphocyte or macrophage series are capable of carrying measles virus.

The viruses isolated from SSPE appear to be variants of measles virus when investigated either in cell cultures (Oyanagi *et al.*, 1971) or when inoculated intracerebrally into hamsters (Lehrich *et al.*, 1970; Albrecht & Schumacher, 1971).

Immunology

Measles antibody was found in the serum and CSF of three patients with SSPE (Connolly *et al.*, 1967). The measles complement fixing (CF) and haemagglutination inhibiting (HI) antibody was at high titre in the serum of two patients and in one patient the titres increased sixteen fold during the course of the illness which indicated an active infection. The titre of measles antibody was much higher than that which follows childhood measles. These findings have since been confirmed by many other investigators (Sever & Zeman, 1968).

The ratio of measles antibody in serum and CSF samples taken simultaneously from the same patient was of some interest. It was found by Clarke, Dane & Dick (1965) that there is a geometric mean ratio of 505 : 1 between the titre of poliovirus antibody in the serum and in the CSF of healthy people. Poliovirus type 2 antibody was used as a marker for an intact blood–brain barrier in the three SSPE patients described above and it was found that the poliovirus type 2 serum/CSF antibody ratios were within normal limits which excluded contamination of the CSF with blood when the samples were taken or a non-specific 'leak' of serum antibody into the CSF. The measles serum/CSF antibody ratios, on the other hand, were low which indicated that measles antibody may be produced or released inside the central nervous system in SSPE (Connolly, 1968).

Connolly, Haire & Hadden (1971) extended these observations and measured measles-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) responses in ten children with measles and in the three patients with SSPE. In the children with measles the measles IgM response had disappeared by the forty-sixth day following the onset of the rash. Measles IgM and IgG were not detected in CSF from five normal patients. The SSPE patients, on the other hand, had abnormally high serum titres of measles IgM and IgG and both measles IgM and IgG were present in their CSF. The measles IgM persisted during prolonged illnesses in serum and CSF which suggested a correlation with the known persistence of measles virus antigen in the brains of the three patients. It was concluded that both measles IgM and IgG may be produced within the central nervous system in SSPE. The origin of the antibody inside the central nervous system is the subject of much speculation but it presumably comes from the perivascular lymphocytes and plasma cells in the brain or in the meninges. It is unlikely that much antibody was derived from cells in the CSF since the cell count in the three cases was within normal limits.

Legg (1967) records a patient with SSPE who made a good recovery, where the measles CF antibody fell to undetectable levels 4 years later but the HI antibody titre had not altered significantly. Serial measles

CF antibody tests may therefore have prognostic value in this disease.

Saunders *et al.* (1969) found specific changes in cell-mediated immunity in a boy with SSPE whose lymphocyte transformation in response to measles antigen was strikingly increased when compared with a healthy matched control. Both boys had had measles. They postulated that immunocompetent lymphocytes specific for measles antigen may interact destructively with host cells in the brain and that this may lead to SSPE.

Non-specific changes in serum and CSF immunoglobulins and cell-mediated immunity have also been described in SSPE (Kolar, 1968; Gerson & Haslam, 1971) but it is not yet known if antibody or cell-mediated immunity play any part in producing the pathological changes in SSPE.

Live measles vaccine

It is disturbing that six children have developed SSPE 3 weeks, 5 months, 1 year (two children) and 3 years (two children) respectively after immunization with live attenuated measles vaccine (Schneck, 1968; Payne, Baublis & Itabashi, 1969; Parker *et al.*, 1970; Gerson & Haslam, 1971; Furesz, 1971). It is therefore essential that careful and prolonged surveillance is maintained on all children who receive the vaccine since this rare complication may not appear until several years later.

Webb, Illavia & Laurence (1971) have propagated measles virus vaccine strains in cultures of non-neuronal cells of human foetal brain and infectious virus was produced for up to 76 days after inoculation. The infected cells proliferated more rapidly than controls but there is no evidence that measles virus produces similar glial proliferation *in vivo* which might lead to SSPE.

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